REMARKS

I. Disposition of the Claims

Claims 41-58 are currently pending in the application. Claims 42, 44-46, 57, and 58 were withdrawn by the Examiner pursuant to an earlier restriction requirement. No claims are cancelled or amended herein.

II. Rejection Under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 41, 43, 49-51, and 53-55 under 35 U.S.C. § 103(a) over Truett (U.S. Pat. No. 5,693,791) in view of Boeckh et al. (*Antimicrobial Agents and Chemotherapy*, 1988, 32:1, pp. 92-95), Renoud-Grappin et al. (*Antiviral Chemistry & Chemotherapy*, 1988, 9, pp. 205-223), and Staroske et al. (*Tetrahedron Letters*, 1998, 39, pp. 4917-4920).

Initially, the Examiner states that Truett teaches the linking of diverse antibiotic moieties via difunctional compounds in order to prepare dimers having the structure A-L-B, where A and B are various antibiotic moieties and L is a linker. *See Office Action*, dated July 7, 2002, p. 3, lines 16-20. Furthermore, the Examiner states that Truett teaches a dimeric compound where one of the antibiotic moieties is ceftazidime, which is a beta-lactam antibiotic that reads on the elected species found in claim 53. *Id.* at p. 4, lines 3-6. The Examiner admits, however, that Truett fails to teach that vancomycin (a glycopeptidic antibiotic) can be used in the disclosed dimers. *Id.* at p. 4, lines 6-7.

To make up for this admitted deficiency, the Examiner cites a combination of three other references, including Boeckh et al., Renoud-Grappin et al., and Staroske et al. The Examiner states that Boeckh teaches that it was well-known prior to Applicants' filing date that ceftazidime and vancomycin could be used in combination to treat bacterial infections. *Id.* at p. 4, lines 8-9.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

With respect to Renoud-Grappin, the Examiner states that it teaches that "one way to achieve effective combination therapy is to covalently link two different drugs." *Id.* at p. 4, lines 15-16. Furthermore, according to the Examiner, this reference teaches that a combination of drugs can be used to "prevent the emergence of drug-resistant virus strains" as well as "three main reasons for combination therapy." *Id.* at p. 4, line 21 - p. 5, line 1. The Examiner admits, however, that Renoud-Grappin deals with compounds that are used for the treatment of human immunodeficiency virus (HIV) and not bacterial infections.

Finally, the Examiner states that Staroske et al. describes dimers of vancomycin and further teaches that such compounds "exhibit improved antibacterial activity." *Id.* at p. 5, lines 11-12.

Based on the combination of all four of these references, the Examiner contends that :

> [I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of Truett concerning the linking of diverse antibiotic moieties combined with the teaching of Boeckh et al [sic] to perform combination therapy using the drugs, the teaching of Renoud-Grappin concerning linking drugs to perform combination therapy and the teaching of Staroske et al [sic] concerning vancomycin dimers linked through the amino and carboxy terminus. . . One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains.

Id. at p. 5, line 17 - p. 6, line 9.

Applicants respectfully traverse the rejection with respect to all claims. Applicants respectfully contend that the rejection of the instant claims under 35 U.S.C.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

§ 103(a) over Truett in view of Boeckh, Renoud-Grappin, and Staroske is improper for at the least the following reasons: 1) the Examiner has failed to establish a proper prima facie case of obviousness; 2) the Examiner has failed to consider all that the references teach, including those portions that teach away from the instant claims and those portions that describe failed experiments; 3) the linking together of a beta-lactam, such as ceftazidime, and vancomycin or its aglycone was contrary to accepted wisdom in the art; 4) the combination of Truett and Boeckh is improper since their combination would render Boeckh unsuitable for its intended purpose; and 5) the Renoud-Grappin reference is non-analgous art and cannot be properly used in combination to render the instant claims obvious.

A. The Examiner has failed to establish a proper prima facie case of obviousness

The Examiner bears the initial burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103(a). M.P.E.P. § 2142. Absent such a showing, Applicants are entitled to a patent. In order to establish a proper prima facie case using a combination of references, the Examiner must show at least the following: 1) there must be a suggestion or motivation that would have led one of skill in the art to modify the cited references to arrive at the claimed invention; 2) there must be a reasonable expectation of success; and 3) the references must teach all the claim limitations. Id. In the instant case, the Examiner has failed to show that the references contain a suggestion or motivation to modify them and that there was a reasonable expectation of success based on the teachings of the references.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

1. The references do not contain a suggestion or motivation to combine them

The Federal Circuit has made clear that "[t]he factual inquiry whether to combine references must be thorough and searching." *In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002). Furthermore, the court has warned against using the teachings in Applicants' own specification to find the claims obvious. In this respect the court stated, "[o]ur case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is *rigorous* application of the requirement for a showing of the teaching or motivation to combine prior art references." *Id.*, quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)(emphasis added). Last, the court has held that the mere fact that the references can be combined or modified does not make such a combination or modification obvious unless the references themselves suggested the desirability of the modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

In this case, the Examiner has cited the general teachings of each of the references and concluded that one of skill in the art would have been motivated to choose particular teachings from each in order to arrive at the instantly claimed compounds that require specific components. Such a conclusion is legal error and ignores the whole of the cited references.

a. The Truett Reference

Truett teaches that two antibiotic moieties can be combined to create a new compound that "can be of value." Col. 1, lines 24-26. Furthermore, Truett teaches that two antibiotic moieties, one of which is known to attack Gram-positive bacteria and the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

other to attack Gram-negative bacteria, can be linked to create a new entity that is "of value." Col. 1, lines 27-30.

Truett discloses a large number of antibiotic compounds that may be linked together according to his invention. In fact, Truett discloses nine general classes of antibiotic compounds and 69 specific compounds within those classes that may be linked together. Truett does not, however, teach that the general class of glycopeptidic antibiotics, of which vancomycin is a member, can be used according to his invention. The fact that Truett discloses a veritable laundry list of antibiotics in the application that was filed in 1995, a time when vancomycin was well-known in the art, yet fails to mention vancomycin or even the general class of antibiotics to which it belongs speaks volumes. The Examiner has not addressed why Truett discloses a laundry list of antibiotics yet fails to disclose an entire class that was well-known in the art at the time of filing. Applicants contend that one skilled in the art reading Truett would have viewed this omission to mean that glycopeptidic antibiotics were not useful in Truett's invention. Accordingly, one skilled in the art would not have been motivated to modify Truett to include vancomycin and arrive at the presently claimed invention.

Furthermore, Truett is completely lacking in guidance as to which classes of antibiotics, much less which species within those classes, should be chosen to afford what the Examiner calls "a broad spectrum antibiotic compound to fight antibiotic resistant strains." As discussed earlier, Truett discloses a laundry list of antibiotics, including sulfonamides, penicillins, cephalosporins, quinolones, chloramphenicol, erythromycin, metronidazole, tetracyclines, and aminoglycosides. Furthermore, only one working example is provided, the linking of p-aminobenzene sulfonamide and

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

sulfapyridine. Col. 45, lines 25-63. Neither of these compounds is a beta-lactam or vancomycin, both of which are required by the instant claims. Moreover, Truett discloses that the compound prepared in the only working example exhibited only "modest inhibition" of certain bacterial cultures. Id.

In the face of this limited guidance, coupled with the report of "modest" results, the Examiner contends that one skilled in the art would have been motivated to prepare a compound of the present claims that require a beta-lactam and vancomycin or its aglycone. Applicants respectfully disagree with this reasoning. Instead, Applicants respectfully submit that one skilled in the art reading the general teachings of Truett would have found nothing to motivate or guide them to prepare a compound containing both a beta-lactam and vancomycin or its aglycone.

Finally, Truett contains no teaching that the disclosed compounds are of use in creating "a broad spectrum antibiotic compound to fight antibiotic resistant strains," as indicated by the Examiner. In fact, Truett contains no teaching at all regarding the treatment of antibiotic-resistant bacterial strains. Instead, the reference only teaches that the disclosed compounds may be useful in treating bacterial infections. Treating run-of-the-mill bacterial infections and treating antibiotic resistant strains are two very different things. *A fortiori*, there is no teaching concerning which of the general classes of antibiotics listed could be advantageously used to create an antibiotic compound useful in treating resistant strains. In sum, the Truett reference does not teach that the disclosed invention is useful for treating antibiotic-resistant bacterial strains. Such motivation is purely speculative on the part of the Examiner and is not based on any

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

teachings in any of the cited references. Such speculation is insufficient to create a prima facie case of obviousness under 35 U.S.C. § 103(a).

b. The Boeckh Reference

Because the Examiner recognizes that Truett is defective, she cites Boeckh et al. for the teaching that ceftazidime, a beta-lactam antibiotic, and vancomycin can be used in combination to treat bacterial infections. The Examiner contends that such a teaching would have motivated one skilled in the art to covalently link these compounds and arrive at the instantly claimed invention. Applicants respectfully disagree with the Examiner's characterization of the teachings of this reference.

Boeckh et al. discloses the administration of ceftazidime and vancomycin in combination to healthy patients. The combination, however, was administered to subjects via separate solutions. See "Dosage" section, p. 92. The reference does not teach or suggest that vancomycin and ceftazidime should be covalently linked together, or even administered in the same solution or at the same time. In fact, as discussed in section B below, the Boeckh reference teaches away from modifying the teachings of Truett to arrive at the instantly claimed invention.

Therefore, one skilled in the art reading the Boeckh reference, in combination with the Truett reference, would not have been motivated to covalently link ceftazidime and vancomycin to arrive at the instantly claimed invention.

c. The Staroske Reference

Staroske et al. teaches the preparation of dimers of vancomycin that are linked through the N- and C-termini. According to the reference, the purpose of preparing such dimers is to take advantage of vancomycin's known antibacterial mechanism of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

action that requires it to dimerize *in vivo*. According to Staroske, linking two vancomycin molecules together may increase its antibacterial activity by overcoming the entropic barrier associated with *in vivo* dimerization. Staroske, however, is deficient in that it does not disclose the use of beta-lactam antibiotics in this strategy. Nor does Staroske teach or suggest covalently linking vancomycin to any other compound besides itself. In fact, as discussed below, Staroske actually teaches away from linking vancomycin to other compounds.

Finally, Applicants respectfully disagree with the Examiner's assertion that Staroske teaches that vancomycin dimers exhibit improved antibacterial activity. The Staroske reference does not contain any teaching regarding the antibacterial activity of the compounds prepared by the authors of the reference. Instead, it only characterizes the antibacterial activity of compounds prepared by others as "insufficiently active for therapeutic use." Such a teaching is, at best, ambiguous regarding any advantage in preparing vancomycin dimers. Therefore, contrary to the Examiner's assertion, Staroske contains no clear teaching that preparing vancomycin dimers has any advantage in the treatment of bacterial infections.

In previous responses, Applicants have contended that Staroske would not have motivated one skilled in the art to arrive at the instantly claimed compounds. See, for example, Response dated March 18, 2002, p. 9, lines 20-25. In response, the Examiner has pointed out that Staroske is being used to show that vancomycin can be chemically modified at specific sites on the molecule. Office Action dated July 2, 2002, p. 6, lines 6-7. In other words, the Examiner is using the Staroske reference to show that methods of chemically modifying vancomycin were known at the time of Applicants'

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

filing and that one skilled in the art was capable of performing such reactions. It is well-established, however, that a prima facie case of obviousness cannot be properly established by simply showing that proposed modifications to the art were within the ordinary skill as of Applicants' filing date. See M.P.E.P. § 2143.01. Instead, the Examiner must make specific findings showing that one skilled in the art would have been motivated to make such modifications. Stated differently, the fact that one skilled in the art could have made a particular modification to a reference does not mean that such a modification would have been obvious. Therefore, Staroske would have taught one skilled in art nothing regarding the instantly claimed invention and certainly would not have motivated one to modify the references to arrive at the instantly claimed invention.

d. The Renoud-Grappin Reference

Finally, the Examiner cites the Renoud-Grappin reference, stating that it teaches successful combination therapy using covalently linked compounds. Applicants continue to maintain that this reference contains no teaching of: 1) antibacterial agents in general; 2) beta-lactams; 3) vancomycin or its aglycone; or 4) a broad spectrum antibacterial agent. Therefore, this reference is completely deficient in terms of teaching one skilled in the antibacterial art anything about preparing antibacterial agents, linked or not. Furthermore, as will be discussed below, this reference is non-analogous art and cannot be used in combination to render the instant claims obvious. Finally, it teaches away from the instantly claimed invention. For all of these reasons, this reference is completely defective and its combination with others does not render the instant claims obvious under 35 U.S.C. § 103(a).

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In sum, it is clear that none of the references, alone or in combination, would have provided sufficient motivation to combine them to arrive at the instantly claimed invention. The Examiner has failed to cite specific teachings that would have motivated one skilled in the art to modify them. Rather, the Examiner has cited only general teachings contained in each reference, and used Applicants' specification as a blueprint, to arrive at a conclusion of obviousness. Such a conclusion is both legal and factual error. Accordingly, Applicants respectfully request that the rejection be withdrawn for all claims.

2. The references do not indicate that one skilled in the art would have had a reasonable expectation of success

In order to establish a prima facie case of obviousness over a combination of references, they must show that one skilled in the art making the proposed modifications would have had a reasonable expectation of success in doing so. This requirement goes to the heart of motivation. If the references do not indicate that particular modifications would be successful for their intended purpose, why would one be motivated to make them?

The Examiner has stated that one skilled in the art reading the references would have been motivated to modify them in order to prepare a "broad spectrum antibiotic compound to fight antibiotic resistant strains." Furthermore, according to the Examiner, ""[o]ne of ordinary skill would have also have had a reasonable expectation of success based on the fact that Staroske et al. teaches linking chemistry for vancomycin." Office Action dated July 2, 2002, p. 6, lines 10-11. Applicants respectfully contend that an

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

expectation of success argument based on the Staroske reference misses the mark and is insufficient to support a prima facie case of obviousness.

With respect to the instantly claimed invention, the proper question is not whether one of skill in the art would have had a reasonable expectation of success in preparing the claimed compounds. Rather, the proper question is whether one of skill in the art, reading the cited references, would have had a reasonable expectation of success in preparing what the Examiner calls a "broad spectrum antibiotic compound to fight antibiotic resistant strains." The Examiner has pointed to no such teachings in the references.

Additionally, Applicants continue to maintain that the Renoud-Grappin reference shows a spectacular failure of the claimed heterodimeric approach in attempting to create an anti-HIV compound useful in the treatment of resistant HIV. In response, the Examiner contends that "[n]o *evidence* has been provided in support of applicant's [sic] conclusion . . . that there is no reasonable expectation of success based on the teachings of the Renoud-Grappin reference." Id. at p. 9, lines 7-10 (emphasis in original). Such argument, however, is an attempt by the Examiner to improperly shift the burden of proof from the Examiner to the Applicant. According to the M.P.E.P., "[t]he examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness." M.P.E.P. § 2142. In this case, Applicants respectfully contend that the Examiner has not made out a prima facie case of obviousness and cannot shift the burden of proof to the Applicants by requiring the submission of evidence of nonobviousness.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Furthermore, the Examiner has agreed that this reference shows a failed approach, stating that "although the teachings of the Renoud-Grappin reference may 'conflict' with respect to the failure of the heterodimeric approach to achieve effective combination therapy, the reference *suggests solutions* . . ." Office Action dated July 2, 2002, p. 8, lines 14-16. Applicants respectfully submit that the Examiner cannot have it both ways. On the one hand the Examiner cannot agree that the evidence of experiments contained in Renoud-Grappin shows a failure of the approach, while at the same time requiring that Applicants submit evidence showing that it was a failure. Applicants maintain their position that the Renoud-Grappin reference shows a failure of the heterodimeric linking approach and one skilled in the art reading it would not have had a reasonable expectation of success of the claimed approach. Accordingly, the Examiner has failed to establish a prima facie case of obviousness and Applicants respectfully ask that the rejection be withdrawn.

B. The references teach away from the instant claims

In making a determination of obviousness under 35 U.S.C. 103(a), the Examiner must consider the references as a whole, including those portions that teach away from the claimed invention. M.P.E.P. § 2141.02. In this case, the Examiner has failed to consider those portions of the cited references that teach away from the claimed invention.

1. The Truett Reference

The majority of the Truett reference is concerned with methods of overcoming problems in the synthesis of compounds in which two antibiotic moieties are covalently linked. There is almost no teaching regarding the antibiotic activity of such compounds.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In fact, Truett contains only one example in which any antibacterial data is provided. Col. 45, lines 25-63. In that example, Truett discloses the linking of para-aminobenzene sulfonamide and sulfapyridine. The resulting product was tested against several bacterial cultures and "[a]ll products showed modest inhibition zones" compared to standard, single antibiotic compounds. Id. This teaching is in direct contrast to the Examiner's assertion that the reference would have motivated one skilled in the art to prepare compounds in which two different antibiotic moieties are covalently linked with the hope of creating "a broad spectrum antibiotic compound to fight antibiotic resistant strains." Simply stated, the experimental results in Truett would have indicated to one skilled in the art that such an approach is not worth pursuing. Therefore, one skilled in the art would have been led away from such a strategy and would not have been motivated to prepare the instantly claimed compounds.

2. The Boeckh Reference

The Boeckh reference would also have led one of skill in the art away from the instantly claimed compounds. Boeckh discuss the problems associated with the intravenous infusion of vancomycin in subjects, including the allergic-type reactions experienced by a significant number of them. These reactions led the authors to modify the manner in which vancomycin was administered to the study subjects. For example, Boeckh states that "[o]n the basis of severe adverse reactions ('red man's syndrome') after the first administration of the 1.0 g dose of vancomycin, the infusion period of this dosage was extended from 1 to 2 h." Boeckh et al., p. 92 (emphasis added). In contrast, Boeckh et al. report that in the same patients, ceftazidime could be administered in a short time period without any significant difficulties. For example, the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

authors write that "[c]eftazidime (2.0 g dissolved in 50 mL of distilled water) was infused constantly over a period of 30 min via another peripheral venous access during the last 30 min of the vancomycin infusion period." Id. (emphasis added). Furthermore, Boeckh et al. report that:

> After administration of 0.5 g of vancomycin with an infusion period of 60 min, 2 of 10 volunteers given vancomycin in combination with ceftazidime compared with none of the volunteers given vancomycin alone developed the typical symptoms, characterized by a rash of the face, neck, upper torso, and upper extremities. With 1.0 g doses of vancomycin over a 60 min infusion period, four of five volunteers developed the typical symptoms. On the basis of these severe adverse reactions, the infusion period was extended from 60 to 120 min at this dosage (1.0 g).

Id. at p. 94.

In other words, because of the difficulties associated with the infusion of vancomycin, Boeckh et al. were forced to administer the two drugs using separate solutions and at different rates. It is clear that Boeckh et al. did not infuse a physical mixture of vancomycin and ceftazidime together or even infuse them at the same rate.

This teaching is in direct contrast to the Examiner's assertion that Boeckh would have led one skilled in the art to prepare compounds in which ceftazidime and vancomycin are used "in combination" by covalently linking them together in the manner claimed. No evidence suggests that such a single molecule would be superior to Boeckh's separate molecules. Instead, one skilled in the art reading Boeckh et al. would have been led away from covalently linking these two drugs to create a single molecule that contains both because doing so necessarily means administering the drugs in the same solution and at the same rate. Such an administration is contrary to the teachings of Boeckh et al. which indicate that a slow, careful, and separate

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

administration of vancomycin and ceftazidime is required to avoid potentially serious adverse events. Furthermore, as discussed below in section D, linking vancomycin and ceftazidime together in the same molecule, in the manner taught by Truett, would have rendered Boeckh unsuitable for its intended purpose.

3. The Renoud-Grappin Reference

Applicants maintain that the Renoud-Grappin reference teaches away from the instantly claimed heterodimeric approach to preparing antibacterial agents because it clearly teaches a failure of the approach in the treatment infectious diseases. Applicants maintain their argument for the reasons of record (see, for example, Response dated March 18, 2002, p. 6, lines 18-30) and for the additional reasons found below.

The reference teaches the preparation of compounds in which a known nucleoside reverse transcriptase inhibitor (nRTI) of HIV-1, so-called d4T, was linked to a non-nucleoside reverse transcriptase inhibitor (nnRTI). The authors explain that such a strategy was based on the detailed structural knowledge of the HIV-1 reverse transcriptase enzyme. In the study, a total of four linked compounds were prepared, labeled 34a-d, in which the length of the linker between the nRTI and the nnRTI was varied. The compounds were tested against several HIV-1 strains, including those known to be resistant to nevirapine, another nnRTI used clinically to treat HIV infections. In addition, d4T and various nnRTI intermediates (34a-d) were tested for antiviral activity.

The antiviral testing results are contained in the reference in Table 2, p. 216. For convenience, a portion of the testing data found in Table 2 is reproduced below.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Compound	HIV-1 IC_{50} (μM) in CEM Cells	CC_{50} (μM) in CEM Cells	Nev^r HIV-1 IC_{50} (μM)	HIV-1 in PBMC IC_{50} (μM)
d4T (nnRTI)	30 ± 9	>100	0.18 ± 0.06	0.05 ±0.03
10 (nnRTI)	0.51 ± 0.03	>10	>10	0.9 ± 0.5
33a (nnRTI)	9 ± 0	>10	ND	>10
33b (nnRTI)	4.3 ± 0	10	ND	>10
33c (nnRTI)	5.8 ± 2.9	10 ± 1	ND	>10
33d (nnRTI)	5.9 ± 2.3	10 ± 1.5	ND	>10
34a (dimer)	9 ± 1.4	61 ± 7	0.083 ± 0.008	0.03 ± 0.02
34b (dimer)	6.3 ± 0.9	>10	0.18 ± 0.14	0.1 ± 0.06
34c (dimer)	8.5 ± 8	26.5 ± 20	0.1 ± 0.04	0.035 ± 0.008
34d (dimer)	6.5 ± 4.2	45.5 ± 8	0.1 ± 0.03	0.04 ± 0.004

From this data, one skilled in the art would learn at least the following: 1) the linked heterodimers were less active against HIV-1 in CEM cells than the parent nnRTI (10) by itself; 2) the linked heterodimers (34a-34d) were not any more active against HIV-1 in CEM cells than the modified nnRTIs (33a-33d); 3) the linked heterodimers were more toxic to CEM cells than were either d4T or the nnRTI alone; 4) the linked heterodimers were not any more active against nevirapine-resistant HIV-1 than was d4T alone; and 5) the heterodimers were not any more active against HIV-1 in PBMC cells than was d4T alone. Based on these conclusions, one skilled in the art would have absolutely no reason to think that linked heterodimers would be any more beneficial in the treatment of HIV-1 infections than either the administration of d4T alone or as a

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

physical mixture with an nnRTI. In fact, the increased toxicity to CEM cells of the dimers versus either d4T or the nnRTI by themselves counsels against the use of such dimers in the clinical treatment of HIV infections.

But, Applicants do not rely solely on their own interpretation of the data presented above for the proposition that this approach failed to deliver a compound with increased activity against HIV-1 versus a single agent or a physical mixture of two agents. Instead, one can look to the conclusions that the authors themselves draw based on their own interpretation of the data presented. For example, Renoud-Grappin et al. make the following statements about the testing results:

- p. 218, column 1: "In TK^- cells, compounds 34a-d were slightly more efficient at inhibiting HIV-1 multiplication than d4T and had a reduced activity compared to compound 10 (Table 2). Nevertheless, it should be noted that in the case of the heterodimers a certain toxicity was measurable and the selectivity indexes were low."

- p. 219, column 1: "It should be noted that, under our experimental conditions involving infected CEM-SS cells, the IC_{50} of heterodimers 34a-d (IC_{50} 0.025 to 0.06 μM) were similar to that for d4T (IC_{50} of 0.059 μM) and therefore we concluded that compounds 34a-d were equipotent to d4T. However, the heterodimers compounds did present some toxicity."

- p. 219, column 1: "This led us to assume that the antiviral effect seen for [d4T]-NH-$(CH_2)_n$-NH-[imidazo[1,5-b]pyridazine] heterodimers was based upon residual activity of the nucleoside moiety, without any contribution of the imidazo[1,5-b]pyridazine spacer monomer. This hypothesis was also sustained by the fact that the heterodimers were (i) inactive against HIV-1 RT activity *in vitro*; and (ii) efficient at inhibiting the multiplication of virus strains resistant to the parent compound **10**."

- p. 219, column 1: ". . . it cannot be excluded that the apparent gain in inhibitory activities of the heterodimers compared to d4T is not specific but results from increased toxicity."

- p. 219, column 2: "The antiviral activity of the heterodimers 34a-d can also be ascribed to the d4T part of the molecule without any significant contribution from the non-nucleoside part."

- p. 219, column 2: "Several reasons may explain the failure of this heterodimer approach to increase the inhibitory activity against HIV."

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

- p. 219, column 2: ". . . the relative inactivity of the heterodimers may be due to poor transport or metabolism of the heterodimers in the host cells used. The heterodimers could have been hydrolytically cleaved either chemically or enzymatically into the nucleoside part. The biological data seem to show that the antiviral activity is present in the nucleoside part."

- p. 219, column 2: "In conclusion, to obtain better insights into the feasibility of the heterodimers approach to increase the efficacy of compounds against RT, chemists should explore other linkers and attachment sites for these linkers on both non-nucleoside and nucleoside analogs."

The testing data in the reference, along with the authors' own characterization of it, point to one inexorable conclusion: the heterodimeric approach described in the reference did not work. Therefore, one skilled in the art reading this reference would not have been motivated to prepare dimeric compounds according to the present claims. Rather, the reference strongly leads away from this approach. Accordingly, Applicants respectfully submit that this reference would have motivated one to avoid modifying the cited references to arrive at the presently claimed compounds. For this reason alone, the rejection of the present claims under 35 U.S.C. § 103(a) should be withdrawn.

In response to Applicants' contention that the Renoud-Grappin reference teaches away from the present claims, the Examiner agrees that it teaches a failure of the heterodimeric approach to combination therapy but insists that it does not teach away from the present invention because it "suggests solutions: 'chemists should explore other linkers and attachment sites for these linkers.'" Office Action dated July 2, 2002, p. 8, lines 14-18. Applicants maintain that these suggestions represent the impermissible "obvious-to-try" standard of obviousness. The obvious-to-try standard is most often found in rejections where the art teaches varying all parameters or trying

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

each of numerous choices until a successful result is obtained, without providing any specific direction or guidance. And as the Federal Circuit has stated, "whether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The Examiner argues that Renoud-Grappin does provide such guidance in the statement that "chemists should explore other linkers and attachment sites for these linkers on both non-nucleoside and nucleoside analogs." Applicants respectfully disagree for the following reasons.

One skilled in the art considering the suggestions of the reference would ask at least the following questions. First, what linkers are appropriate to explore in terms of preparing antibacterial or anti-HIV agents? The Renoud-Grappin reference does not deal with antibacterial agents at all, so one would have to look to the Truett reference for guidance. But Truett provides no guidance either, because it discloses at least 5 general classes and 23 specific types of linkers. Would the use of each of these linkers provide antibacterial compounds with the desired activity? Second, what other "attachment sites" on each component of the heterodimer should be explored? For example, in nucleoside analogs the linker may attach through either the sugar portion or the heterocyclic base portion of the compound. If one chooses to link through the sugar portion, should the linkage be through the 2', 3', 4', or 5' position? If through the 5' position of the sugar, should the 5'-hydroxyl group of the sugar remain unsubstituted so that it can be phosphorylated *in vivo* to the corresponding triphosphate or is phosphorylation unnecessary? Will the binding of the non-nucleoside analog interfere with phosphorylation of the nucleoside analog portion of the heterodimer, if such phosphorylation is necessary for activity? Third, where on the non-nucleoside analog

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

should the linkage occur? Fourth, what nucleoside and non-nucleoside analogs should be used that would afford a dimeric compound with the appropriate balance of activity against wild-type HIV, nucleoside-resistant HIV, and non-nucleoside resistant HIV, and at the same time show minimal cellular toxicity so that it can be used chronically in HIV-infected patients? The answer to each of these questions represents an involved research project all its own. Neither the Truett or Renoud-Grappin references provide any guidance to one skilled in the art as to which of the many parameters indicated above should be varied, or how they should be varied, in order to obtain a compound with the desired activity. Instead, the statement is merely a suggestion to experiment and is the type of obvious-to-try rationale the Federal Circuit has warned is an insufficient basis to support a rejection under 35 U.S.C. § 103(a).

4. The Staroske Reference

Finally, the Examiner has failed to consider that portions of the Staroske reference teach away from the presently claimed invention. As discussed earlier, Staroske states that certain glycopeptidic antibiotics, including vancomycin, are known to dimerize *in vivo* and that such dimerization is critical to their antibacterial activity. This known propensity of vancomycin to dimerize *in vivo* provided the rationale for preparing the covalently linked vancomycin dimers disclosed in the reference.

With that in mind, one skilled in the art reading this reference would not have been motivated, for several reasons, to prepare compounds in which vancomycin is tethered to any other compound. First, according to the reference itself, the entire rationale for preparing vancomycin dimers is to overcome the entropic barriers associated with vancomycin's *in vivo* dimerization. There is no suggestion or teaching

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

in the reference that linking vancomycin to any other compound would improve its antibacterial activity. In fact, one skilled in the art reading Staroske could conclude that doing so would interfere with vancomycin's ability to dimerize, thereby decreasing its usefulness as an antibiotic. Contrary to the Examiner's assertion, Staroske does not provide a general teaching that linking vancomycin to any other antibiotics would provide a useful compound.

In summary, all of the references cited by the Examiner in support of the rejection of the current claims under 35 U.S.C. § 103(a) contain teachings that would have led one skilled in the art away from the instantly claimed invention. The one compound reportedly prepared in Truett did not exhibit increased antibacterial activity compared to its individual components, portions of Boeckh teach that vancomycin and ceftazidime should be administered in separate solutions and at differing rates, Renoud-Grappin teaches that their heterodimeric approach was a failure, and it was known in the art at the time of filing that vancomycin exerts its antibacterial effect by dimerizing *in vivo*. None of these references, alone or in combination, would have motivated one skilled in the art to prepare the instantly claimed compounds. Accordingly, the Applicants respectfully request that the rejection be withdrawn with respect to all claims.

C. The presently claimed invention was contrary to accepted wisdom in the art

When rejecting a claimed invention as obvious under 35 U.S.C. § 103(a), the Examiner must consider the prior art as a whole. Evidence that Applicants proceeded contrary to accepted wisdom in the art is powerful evidence of non-obviousness. M.P.E.P. § 2145(X)(D)(3). In the instant case, Applicants proceeded contrary to

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

accepted wisdom in the art by linking a beta-lactam, such as ceftazidime, with vancomycin or its aglycone.

At the time the instant application was filed, it was accepted wisdom in the antibacterial art that vancomycin solutions were incompatible with certain other drugs, including ceftazidime. Evidence of this knowledge appears in the *Physicians' Desk Reference*, which states that:

> Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines (with one of the compatible IV fluids) between the administration of these two agents.

Physicians' Desk Reference, 53rd Edition, 1999, p. 1133 (attached herein as Appendix A).

With this knowledge in mind, Applicants respectfully submit that it would not have been obvious to one skilled in the art to combine a beta-lactam antibiotic and vancomycin or its aglycone into the same molecule. Such a molecule, when present in solution, necessarily places a ceftazidime-like moiety in the same solution as a vancomycin-like moiety. One skilled in the art reading the *Physicians' Desk Reference* would not have thought that such a molecule would be physically stable enough to be useful. Therefore, Applicants claimed compounds in which a beta-lactam antibiotic, such as ceftazidime, is covalently linked to vancomycin or its aglycone would not have been obvious to one skilled in the art at the time the instant application was filed. Accordingly, Applicants respectfully request that the rejection be withdrawn with respect to all claims.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

D. The combination of Truett and Boeckh would have rendered Boeckh unsuitable for its intended purpose

Generally, the Examiner should not combine references to find an invention obvious under 35 U.S.C. § 103(a) when they teach away from their combination or when the combination would render the references unsatisfactory for their intended purpose. See M.P.E.P. § § 2145(X)(D) and 2145(X)(D)(2). In this case, both Truett and Boeckh teach away from their combination. Additionally, their combination would render Boeckh unsuitable for its intended purpose.

The Truett reference teaches covalently linking two antibiotics using a suitable linker. Most importantly, Truett teaches linking such compounds only in a 1:1 ratio. For example, Truett states that the "invention is concerned with simple methods of preparing a large number of new and novel structures possessing a wide range of antibiotic activity via linking together two antibiotic moieties." Col. 1, lines 47-50 (emphasis added). Second, Truett teaches that the disclosed compounds can be prepared using the following linking agents: 1) diisocyanates; 2) dianhydrides; 3) diacidchlorides; 4) diepoxides; and 5) carbodiimides. Col. 5, lines 42-60. Third, Truett discloses specific linking agents that can be used beginning in col. 22, line 11 through col. 25, line 14. All of them are only capable of linking two different moieties together. Fourth, Truett provides general examples describing the preparation of such compounds beginning in col. 25, line 19 through col. 31, line 52. In each of these descriptions, no more than two antibiotic moieties are linked together in a single molecule. Finally, in the one example in which a compound was actually prepared, col. 45, lines 26-63, one molecule of para-aminobenzene sulfonamide is linked to one molecule of sulfapyridine. Therefore, based on this disclosure, one skilled in the art

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

would have understood that Truett discloses only compounds that contain no more than a 1:1 ratio of two different antibiotic compounds. Nowhere does Truett teach or suggest more than a 1:1 ratio of antibiotic compounds or that more than two moieties can be attached to each linker.

In contrast, Boeckh explicitly teaches other than a 1:1 ratio of ceftazidime and vancomycin. For example, the reference reports the administration of vancomycin alone or in combination with ceftazidime. When administered together, 0.5 g of vancomycin and 2.0 g of ceftazidime were used. According to the *Physicians' Desk Reference*, the molecular weight of vancomycin hydrochloride, suitable for IV administration, is 1,485.73 and for ceftazidime is 636.6 (*Physicians' Desk Reference*, 53rd Edition, 1999, pp. 1635 and 1130, respectively). A simple calculation shows that 0.5 g of vancomycin is approximately 0.34 mmoles [(0.5/1485.73) x (1000) = 0.34 mmoles] and 2.0 g of ceftazidime is approximately 3.14 mmoles [(2.0/636.6) x (1000) = 3.14 mmoles]. Therefore, Boeckh teaches at best that the use of a combination of vancomycin and ceftazidime to inhibit bacterial growth is useful when they are used in about a 1:9 ratio. This is far from the 1:1 ratio taught by Truett.

Furthermore, Boeckh teaches that more than a 1:1 ratio of ceftazidime to vancomycin is required for sufficient and therapeutic antibacterial activity. On page 93, the reference teaches the minimum inhibitory concentrations (MICs) of both ceftazidime and vancomycin against several bacterial strains. The MICs are defined as the minimum concentration of each compound required to inhibit visible bacterial growth. An examination of the data clearly shows that, depending on the particular bacterial strain being tested, either more vancomycin than ceftazidime or more ceftazidime than

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

vancomycin was required to inhibit bacterial growth. For example, against *S. aureus*, Boeckh et al. report that 1-2 µg/mL of vancomycin (1 µg/mL = 6.73 x 10^{-4} µmoles/mL) and 8-16 µg/mL of ceftazidime (8 µg/mL = 0.013 µmoles/mL) were required to prevent visible bacterial growth. This is a 1:19 ratio of vancomycin to ceftazidime required to exhibit an effective antibacterial effect. Alternatively, greater than or equal to 128 µg/mL of vancomycin (0.086 µmoles/mL) are required to inhibit the growth of *P. aeruginosa*, while only 1 to 16 µg/mL of ceftazidime (0.002 to 0.025 µmoles/mL) were required to inhibit the same bacterial strain, a ratio of approximately 43:1 to 3.4:1 of vancomycin to ceftazidime.

Consideration of this data shows the Examiner's faulty logic in combining the teachings of Truett and Boeckh. On the one hand, Boeckh clearly shows that when vancomycin and ceftazidime are used in combination, flexibility in dosing is required in order to effectively treat certain types of bacterial infections. In contrast, Truett teaches none of that flexibility and instead is limited to the preparation of compounds containing a 1:1 ratio of antibiotic moieties.

It is clear that these two teachings cannot be reconciled. Furthermore, to combine these teachings is to proceed in a manner that is contrary to the Examiner's purported motivation to produce a "broad spectrum antibiotic compound to fight antibiotic resistant strains." For example, assume a subject is infected with both *S. aureus* and *P. aeruginosa* bacterial strains and one skilled in the art wished to treat both infections with a combination of vancomycin and ceftazidime. In doing so, one would wish to minimize possible toxicological risks to the subject by administering the minimum amount of each compound necessary to inhibit the growth of the two bacteria.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Based on the MICs provided by Boeckh, approximately 6.73 x 10^{-4} µmoles/mL of vancomycin is needed to inhibit *S. aureus* while approximately 0.002 to 0.025 µmoles/mL of ceftazidime is needed to inhibit *P. aeruginosa*. This affords a ratio of vancomycin to ceftazidime of approximately 1:3 to 1:37. If the teachings of Truett were followed and the minimum amount of a compound comprising a 1:1 ratio of vancomycin to ceftazidime were administered to a subject to treat the *S. aureus* infection (6.73 x 10^{-4} µmoles/mL), too little vancomycin and ceftazidime would be administered to fight the *P. aeruginosa* infection (6.73 x 10^{-4} µmoles/mL delivered versus the 0.002 to 0.025 µmoles/mL required). The administration of such sub-therapeutic doses would most likely create antibacterial resistance in a subject, which is the opposite result contemplated by the Examiner. Alternatively, if one wished to treat a *P. aeruginosa* infection by administration of a compound containing a 1:1 ratio of vancomycin to ceftazidime, one would administer 0.002 to 0.025 µmoles/mL. Administration of this amount, however, represents the administration of much more vancomycin than is required to fight the *S. aureus* infection (only requires 6.73 x 10^{-4} µmoles/mL but 0.002 to 0.025 µmoles/mL would be administered). Owing to the known toxicological problems associated with the administration of vancomycin (see Boeckh et al., pp. 92 and 94 for example) it would be undesirable to administer more vancomycin than is necessary.

All of these problems, however, can be overcome by using separate, unlinked compounds in which the number of vancomycin and ceftazidime molecules can vary depending on the bacterial infection sought to be inhibited. In the above example, for instance, one skilled in the art would wish to prepare a mixture containing approximately

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

1 molecule of vancomycin for every 9 or 10 molecules of ceftazidime. The administration of such a mixture would, according to the data presented in Boeckh, afford a therapeutically effective amount of vancomycin and a therapeutically effective amount of ceftazidime. In contrast, Truett does not teach such flexibility and only teaches compounds that comprise a 1:1 ratio of two different antibiotics. Nowhere does Truett suggest or teach compounds comprising more than a 1:1 ratio of such compounds attached to a single linker.

In summary, both the Truett and Boeckh references teach away from their combination. In addition, such a combination would render Boeckh unsuited for its intended purpose of treating a wide variety of bacterial infections using a physical combination of vancomycin and ceftazidime in which the dose of each can be varied depending on the infection being treated. Accordingly, these references cannot be properly combined to render the instant claims obvious under 35 U.S.C. § 103(a) and Applicants respectfully ask that the rejection be withdrawn.

E. The Renoud-Grappin reference is non-analogous art and cannot properly be used in combination to find the instant claims obvious under 35 U.S.C. § 103(a)

In general, a reference cannot be properly used in combination to find a claimed invention obvious under 35 U.S.C. § 103(a) if the reference is non-analogous art. M.P.E.P. § 2141.01(a). According to the Federal Circuit, a reference is considered analogous art if two criteria are satisfied: 1) if the art is from the same field of endeavor; and 2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to the particular problem to be solved. *See Wang Laboratories, Inc. v. Toshiba Corp.*, 993 F.2d 858, 864 (Fed. Cir. 1993). A finding that art is non-analogous

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

means that it cannot be used to render the claims at issue obvious under 35 U.S.C. § 103(a). *Id.* In this case, the Renoud-Grappin reference does not satisfy either criteria because it is not in the same field of antibacterials and is not reasonably pertinent to the problem of the preparation of effective antibacterial agents because it concerns antiviral compounds.

The instantly claimed compounds are useful as antibacterial agents. According to *Stedman's Medical Dictionary*, bacteria are defined as:

> A unicellular prokaryotic microorganism that usually multiplies by cell division and has a cell wall that provides a constancy of form; they may be aerobic or anaerobic, motile or nonmotile, and free-living, saprophytic, parasitic, or pathogenic . . . .

Stedman's Medical Dictionary 183 (26th ed. 1995). In contrast, viruses are:

> . . . a group of infectious agents which with few exceptions are capable of passing through fine filters that retain most bacteria, are usually not visible through the light microscope, lack independent metabolism, and are incapable of growth or reproduction apart from living cells. They have a prokaryotic genetic apparatus but differ sharply from bacteria in other respects. The complete particle usually contains only DNA or RNA, not both, and is usually covered by a protein shell or capsid that protects the nucleic acid.

Id. at 1939 (Pages attached herein as Appendix B). Considering these definitions, it is clear that one skilled in the art would not consider the preparation of effective antibacterial agents to be in the same field of endeavor as the preparation of effective antiviral agents; the differences between bacteria and viruses are simply too great to draw any analogies between them. Also, compounds that are effective against bacterial infections are generally completely ineffective against viral infections. In fact, the misuse of antibacterials in patients suffering from viral infections is believed to be one of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

the leading causes of bacterial resistance, a major, present-day health concern. As the Food and Drug Administration has written in educational materials, "[a]ntibiotics kill bacteria, not viruses." Ricki Lewis, *The Rise of Antibiotic-Resistant Infections*, FDA Consumer Magazine (Sept. 1995), at http://www.fda.gov/fdac/features/795_antibio.html (Attached herein as Appendix C). Therefore, the Renoud-Grappin reference does not meet the first criteria of analogous art because it is not in the same field of endeavor as the presently claimed invention.

Furthermore, the Renoud-Grappin reference does not satisfy the second criteria of analgous art because the information it discloses is not reasonably pertinent to the particular problem that the present invention solves. As discussed earlier, bacteria and viruses differ in many important respects. These differences include, but are not limited to: 1) bacteria are considered living organisms while viruses are not; 2) bacteria multiply by cell division while viruses multiply using the host-cell genetic machinery; and 3) bacteria have cells walls while viruses are not at all cellular in nature. These differences are especially critical in the instant case wherein the claimed invention is a series of novel, effective, antibacterial agents that act by preventing bacterial cell wall synthesis. In contrast, the anti-HIV compounds disclosed in the Renoud-Grappin reference function by inhibiting the HIV reverse transcriptase enzyme, an enzyme that bacteria do not contain and of which no counterpart in the antibacterial art is known. Finally, one skilled in the art would not expect the compounds disclosed by the Renoud-Grappin reference to be effective as antibacterial agents because they exert their antiviral effects via a completely different, non-analogous mechanism of action.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Therefore, because the Renoud-Grappin reference is not in the same field of endeavor and is not reasonably pertinent to the problem being solved, it is non-analogous art and cannot be properly used to find the presently claimed invention obvious under 35 U.S.C. § 103(a). For this reason, Applicants respectfully submit that a linking strategy with respect to a beta-lactam antibiotic and vancomycin or its aglycone would not have been obvious to one skilled in the art at the time the present invention was made. Accordingly, Applicants respectfully ask that the rejection be withdrawn.

III. Conclusion

In conclusion, Applicants respectfully contend that the Examiner has failed to establish a prima facie case of obviousness under 35 U.S.C. § 103(a) with respect to the present claims in view of Truett, Boeckh, Renoud-Grappin, and Staroske because: 1) the Examiner has failed to point to specific teachings in the references that would have motivated one skilled in the art to combine them; 2) the references teach away from the instantly claimed invention; 3) the presently claimed invention was contrary to accepted wisdom in the art at the time it was made; 4) the combination of Truett and Boeckh is improper because it renders Boeckh unsuitable for its intended purpose; and 5) the Renoud-Grappin reference is non-analogous art. For all these reasons, Applicants respectfully request that the rejection be withdrawn for all claims.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 15, 2003

By: Allen M. Sokal
Allen M. Sokal
Reg. No. 26,695

555119_1.DOC

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com